

# Modern Alternative or First-line Treatment: How to Safely Use Negative Pressure Wound Therapy in Diabetic Foot Syndrome?

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## REVIEW

**Abstract**—Clinical experience and basic science studies show that Negative Pressure Wound Therapy (NPWT) is a promising yet still under-used treatment method for patients with diabetic foot syndrome. Despite its advantages, it may carry the risk of serious side effects if the indications and contraindications are not strictly observed. The aim of this article is to discuss myths and facts about NPWT in conditions such as inadequate blood supply, insufficient wound debridement, osteomyelitis or the necessity to monitor laboratory parameters during the therapy. We will try to define the optimal conditions for NPWT in order to obtain better results and eliminate the risk of side effects.

**Keywords**—negative pressure wound therapy, vacuum therapy, diabetic foot syndrome, diabetic ulcer

### I. INTRODUCTION

**D**IABETIC foot syndrome (DFS) is a growing concern of modern medicine. It affects approximately 10–15% of patients with type 2 diabetes (DM). This number is consistently growing due to aging population and decreasing the age of DM onset.<sup>1</sup> Chronicity and natural predisposition to wound infection in DFS determine the need for optimization of the healing process. NPWT is effective in restoring moisture balance in the wound bed, improving blood supply to damaged tissues and eliminating the source of infection. It promotes the formation of granulation tissue and finally accelerates wound closure.<sup>2</sup> DFS can be the cause of generalized infection and even death of the patient. The most common life-threatening complication is amputation. 5-year mortality rate after first amputation is approx. 40%, which is similar to e.g. kidney cancer mortality rate.<sup>3, 4</sup>

### II. HOW DO THE GUIDELINES PRIORITIZE NPWT IN THE TREATMENT OF DFS?

Standardized indications for NPWT in the DFS were published recently in 2011 by NPWT-Expert Panel. They define two main goals of DFS patients' treatment.<sup>5</sup> The primary aim is the wound closure. Of all indications, the strongest

recommendation is given to NPWT as a second-line treatment of non-healing wounds and managing surgical wounds of 2nd and 3rd grade in Texas Scale<sup>6</sup> in DFS without ischemia. The secondary goal is stopping the wound progression (degree of recommendation B). The guidelines emphasize the importance of NPWT as a method that fulfils the task of preventing the amputation and re-amputation of the limb and has an indirect influence on mortality of patients after amputations. It should be considered in every patient with DFS. Before the treatment, however, one should carefully analyse all the contraindications and answer some key questions about the patient. These issues will be discussed below.

#### A. Can NPWT be used in patients with neuro-ischemic DFS?

NPWT increases levels of TGF- $\beta$  and PDGF, accelerates the formation of granulation tissue and amplifies angiogenesis.<sup>7</sup> Xia observed an increase of VEGF, EGF, PDGF and angiotensin-2 concentration and reduction of fibroblast growth factor level.<sup>8</sup> Furthermore, NPWT mechanically contributes to optimizing the perfusion at a negative pressure of  $-125$  mmHg.

According to Timmers, the hypoperfusion occurs only at a negative pressure below  $-500$  mmHg.<sup>9</sup> Kasai draws the hypothesis that the suction pressure contributes to the occlusion of the majority of the capillary vessels located on the edge of the wound.<sup>10</sup> Present studies show that even negative pressure of  $-125$  mmHg will produce a zone of increased perfusion (2.5 cm) as well as ischemic zone within and immediately around (0.5 cm) the edges of the wound. Temporary ischemia can promote healing through hypoxia inducible factor (HIF) production.<sup>11</sup> Borgquist demonstrates that using lower levels of negative pressure of  $-80$  mmHg does not have an influence on the therapeutic effect.<sup>12</sup> In patients with impaired blood flow in the lower limb arteries, optimal negative pressure levels can cause the necrosis in the wound edges.<sup>13, 14</sup> This is because patients with an ankle-brachial index (ABI) of less than 0.6 should not be considered for the NPWT. The T<sub>pO</sub><sub>2</sub> measurement should be the diagnostic method of choice, but it is not widely available. Levels below 30 mmHg limit the use of NPWT. Every patient with clinically significant arterial occlusions should first undergo revascularization procedures.

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### B. Can we substitute debridement by NPWT?

The proper wound treatment requires a comprehensive approach. The guidelines for wound management were published in 2002 by European Wound Management Association (EWMA). According to the TIME concept, comprehensive care of wound bed consists of tissue management, control of infection and inflammation, moisture balance and advancement of the epithelial edge of the wound.<sup>15</sup> NPWT fits perfectly into the above-mentioned strategy, which is extremely important in the treatment of DFS ulceration. It should be noted, that proper preparation and debridement of the wound is essential before the treatment. Removal of necrotic tissue and bacterial burden helps to define the size and condition of the wound. We emphasize that in neuropathic ulcers the superficial, hyperkeratotic layer can cover the infected tissues. Deep debridement can reveal bare bone fragments, thus limiting the use of traditional NPWT systems. Minimization of the infection potential and prolonged inflammatory process induced by pro-inflammatory factors from necrotic tissue contributes to the optimization of the treatment conditions. To sum up, NPWT sticks to the TIME concept, provided that the deep debridement before the treatment is achieved.

### C. How does NPWT system control the presence of infection signs in the wound?

The amount of exudate in chronic wounds is increased and leads to maceration of surrounding tissues. The composition of the fluid is also imbalanced, with increased level of pro-inflammatory factors. Chronic inflammation in the wound bed is expressed through the high levels of TNF- $\alpha$ , IL-1 $\beta$  and IL-6 in the exudate.<sup>16–18</sup> It is proven that an increase in the level of Il-1 and a reduction of TGF- $\beta$  induces higher expression of metalloproteinases (MMP). The levels of MMP are increased in diabetic ulcers. Many researchers have observed a significant prevalence of MMP-9 and MMP-2.<sup>19–21</sup> The healing and remodelling processes can be inhibited by an inadequate ratio of metalloproteinases to their tissue inhibitors (TIMP).<sup>22</sup> Hyperglycaemia, often accompanying diabetic foot ulcers, leads to further development of inflammation through the activation of mitogen-activated protein kinase and protein kinase C, as well as oxidative stress and AGEs.<sup>23</sup> Removal of an excess volume of exudate and MMP in NPWT is likely to increase the healing rate and tissue regeneration.<sup>24</sup>

The additional benefit in wounds associated with abundant exudate is the physical decompression of the pressure on the wound bed. According to Young, in 4 days of NPWT swelling was decreased by 43%. This can be explained by macro-deformation of the tissues, leading to reverse tissue expansion and also altering the blood flow in the wound vessels.<sup>25</sup> Numerous studies show that the addition of exudate from chronic wounds to the cell culture inhibits the proliferation of the cells.<sup>18, 26, 27</sup>

Mechanical suction in NPWT reduces swelling and also allows controlling the infection by decreasing number of microorganisms and dead cells, which can cause prolonged inflammation and lack of wound healing.

NPWT is indicated especially in wounds involving extensive exudate that is difficult to manage. "Dry wounds" (the amount of aspirate 20–50 mL/day) require special care and considering a method other than NPWT.

### D. Does the exudate removal reduce the amount of infectious agent in the wound?

A clinical infection in the wound bed and adjacent tissues is a major problem leading to persistent inflammation and significantly delayed healing process. Undoubtedly, improving blood circulation and function of inflammatory cells in NPWT contributes to the proper management of infected wounds. This is why patients with grade I and II in PEDIS scale can benefit the most from using NPWT. According to the research by Moues and Weed, in animal model of chronic wounds, the number of bacterial colonies has not diminished during NPWT.<sup>28, 29</sup> The bacterial profile, however, has changed from anaerobic to aerobic G+ species. According to studies, *S. aureus* is the dominating microorganism in ulcers treated with vacuum therapy.<sup>29</sup> It appears that the colonization by *S. aureus* may have a positive effect on the wound healing.<sup>30, 31</sup> There is a discussion on the possible negative effect of foams used in NPWT and their role in spreading the infection, which may result from the problem of foam contamination.<sup>32</sup> NPWT-EP recommends repetitive changes of the NPWT dressings every 2 or 3 days. Special attention should be given to signs of infection and fibres of dressing left in the wound. Foam or gauze dressings can be used. According to recent publications, both types of dressing are equally effective at delivering negative pressure, wound contraction and stimulation of blood flow at the wound edge. The advantage of gauze is its fast application and easy adjustment to the surface of wounds. In contrast to foam dressing, application of gauze may be quite challenging in the case of a complex wound with several layers and uneven bed.<sup>33</sup> However, studies have documented an in-growth of granulation tissue into the cells of the open cell polyurethane foam. This may cause patients to experience pain during dressing changes and disturb the re-epithelialisation process.<sup>34–37</sup>

Proper wound healing by granulation may be inhibited by the remaining fibres of the dressing. Using wound contact layers helps eliminate in-growth and pain.<sup>38</sup> The NPWT method is based on the induction of negative pressure in purified wounds and it is natural that after discontinuation of drainage the production of exudate may be increased. The sponge used in NPWT should be prepared with special attention in order to avoid covering healthy skin with the dressing. Too large sponge may damage the healthy skin around the wound and increase the risk of wet necrosis or fistula formation. Local allergic reactions were also observed in NPWT patients, manifesting as pruritus or contact eczema (e.g. contact dermatitis caused by the film covering the sponge). It is only rarely that the therapy has to be discontinued, especially in cases of uncontrolled bleeding or a blood clot formation under the dressing.

### E. Is osteomyelitis a contraindication for NPWT in DFS?

The development of inflammation and infection during the NPWT may be overlooked. Anatomy of the foot allows rapid spread of infection along the muscles and tendons.<sup>39</sup> Special attention should be given to osteomyelitis, which requires chronic anti-microbial therapy or surgical resection. The risk of osteomyelitis increases when the ulcer is not healing after six weeks of proper therapy. Clinically, osteomyelitis can be confirmed in the case of a deep, extensive ulceration when the bone is visible at the bottom of the wound bed or when the PTBT test is positive. The local ischemia caused by NPWT could increase the area of infection when osteomyelitis is present. In case of extensive infections (defined as grade 3 and 4 on a PEDIS scale), standard NPWT systems should not be used. Before the NPWT, osteomyelitis needs to be ruled out in order to prevent bacterial translocation from the wound bed to bone.<sup>40</sup> In patients with osteomyelitis, NPWT should not be initiated until the appropriate antibiotic therapy and the wound debridement have been performed, including removal of infected bone if necessary.<sup>41</sup>

### F. What laboratory parameters should be monitored during NPWT?

Chronic wounds are conducive to developing anaemia. Patients with DFS are extremely prone to ischemia. Physicians should take care that the levels of haemoglobin stay optimal and not fall below 10 g/dL. Emphasis on this parameter reduces the likelihood of ischemic episodes and allows the wound to heal properly. Patients on chronic anticoagulant therapy, as well as patients with active bleeding in medical history or bleeding disorders, require increased attention due to the bleeding risk. However, the use of anticoagulants is not a contraindication to NPWT.

### G. Does NPWT system induce neoplastic process?

It should be noted that increased perfusion may be a problem in wounds with neoplastic lesions. To minimize the risk of uninhibited tumour growth, patients with atypical ulcerations and malignancies in other organs should be screened for the presence of neoplastic cells in wound bed before the NPWT treatment.<sup>42</sup>

## III. CONCLUSIONS

NPWT reduces the number of required dressing changes and allows the patient to rest.<sup>43</sup> Fewer interventions in the wound decrease the likelihood of contamination.<sup>44</sup> Moreover, the change of dressing used in vacuum therapy is less painful for patients. At the beginning of the therapy, however, patients could feel pain or discomfort due to the negative pressure. The vacuum stimulates the growth of new tissue and epithelialization. It contributes to the well-being of the patient since the first results are soon visible.<sup>45</sup> In addition, negative pressure continuously removes the excess of exudate, which reduces odour from the wound.<sup>46</sup> However, NPWT must be applied for at least 22 hours a day to yield such results.

NPWT enables the concomitant rehabilitation, which shortens the period of treatment.<sup>47</sup>

So far, NPWT was considered an expensive technical novelty but it has a significant advantage in terms of relative cost-effectiveness in comparison with conventional therapy. Care for patients with active ulcer multiplies the expenses incurred by the health care system (5.4 times compared to patients with isolated DM).<sup>48</sup> Wound closure reduces the amount of spending for proper wound management. It should be noted that the treatment of superficial infection is approx. 11 times cheaper than in the case of generalized infection which often results in the need for amputation. Reduced frequency of dressing changes, faster wound healing and the possibility of mobilization of patients at the same time, lowers the cost of vacuum treatment compared to standard therapy.<sup>49</sup>

Growing knowledge on the mechanism of action of standard NPWT increases the safety of this therapy in patients with DFS. The best results of NPWT are observed in patients with DFS in grade 2nd and 3rd in Texas Scale. Ischemic wounds before revascularization are a contraindication for this therapy. To stop the infection from spreading, it is recommended to change foam and gauze every 2–3 days. Special care is advised while changing dressings to avoid in-grows of granulation tissue into the dressing. Monitoring of morphology parameters is indicated before and during the therapy. When lengthy healing is observed, histopathological assessment is advised to exclude malignancy. A comprehensive treatment of the patient involving both standard methods and NPWT significantly increases the chances of saving the affected limb.

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